Answer 1:

Bibliographic Information

Pregnenolone stimulates LNCaP prostate cancer cell growth via the mutated androgen receptor. Grigoryev, Dmitry N.; Long, Brian J.; Njar, Vincent C. O.; Brodie, Angela H. M. Department of Pharmacology and Experimental Therapeutics, Health Science Facility, University of Maryland School of Medicine, Baltimore, MD, USA. Journal of Steroid Biochemistry and Molecular Biology (2001), Volume Date 2000, 75(1), 1-10. Publisher: Elsevier Science Ltd., CODEN: JSBBEZ ISSN: 0960-0760. Journal written in English. CAN 134:232010 AN 2001:183923 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Pregnenolone (P5), a common precursor of many steroids, is present in the blood of normal adult men at concns. of 1-3 nM. In vitro, P5 was found to stimulate LNCaP-cell proliferation 7-8-fold at a physiol. concn. (2 nM), and 3-4-fold at a subphysiol. concn. (0.2 nM). Growth stimulation at the 2-nM concn. was comparable with that of the androgen, dihydrotestosterone at its physiol. concn. (0.5 nM; 9-10-fold increase in cell no.). To det. whether P5 or its metabolites were mediating this growth response, LNCaP cells were incubated with [3H]P5 and high-performance liq. chromatog. (HPLC) was performed. After a 48-h exposure, two unidentified metabolites were detected. Although, the P5 metabolites slightly increased LNCaP-cell growth in vitro, their effect was significantly less than P5 alone, suggesting that the growth stimulation was mediated by P5 itself. We further showed that P5 sustained its proliferative activity in vivo and stimulated the growth of LNCaP-tumor xenografts in intact male SCID mice as well as in castrated animals. In order to det. whether P5 was binding to a specific site in LNCaP cells, receptor binding studies were performed. Scatchard anal. predicted for a single class of binding sites with Kd = 1.4 nM. Studies were performed to det. the effects of P5 on transcription mediated by wild-type and LNCaP androgen receptors. P5 was shown to activate transcription through the LNCaP androgen receptor (AR), but not the wild-type AR. This implies that P5 most likely stimulates LNCaP-cell proliferation through binding to the cellular mutated AR present in LNCaP cells. We have also demonstrated that drugs designed to be antagonists of the androgen, progesterone and estrogen receptors, and one of our novel compds. designed to be an inhibitor of androgen synthesis, were potent inhibitors of the AR-mediated transcriptional activity induced by P5, and were able to inhibit LNCaP-cell proliferation.

These findings suggest that some prostate cancer patients who appear to become hormone-independent may have tumors which are stimulated by P5 via a mutated AR and that these patients could benefit from treatment with antiestrogens, antiprogestins, or with some of our novel androgen synthesis inhibitors.

Answer 2:

Bibliographic Information

Pharmacological therapy of keloids in an athymic mouse model. Blazek J; Ottomann C; Muehlberger T Abteilung fur Plastische Chirurgie und Handchirurgie, DRK-Kliniken Berlin-Westend. t.muehlberger@drk-kliniken-westend.de Handchirurgie, Mikrochirurgie, plastische Chirurgie : Organ der Deutschsprachigen Arbeitsgemeinschaft fur Handchirurgie : Organ der Deutschsprachigen Arbeitsgemeinschaft fur Mikrochirurgie der Peripheren Nerven und Gefasse : Organ der Vereinigung der Deutschen Plastischen Chirurgen (2008), 40(2), 81-7. Journal code: 8302815. ISSN:0722-1819. (COMPARATIVE STUDY); (ENGLISH ABSTRACT); (EVALUATION STUDIES); Journal; Article; (JOURNAL ARTICLE) written in German. PubMed ID 18437665 AN 2008275169 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

PURPOSE: In spite of the high incidence of dermal fibroproliferative disorders, there is no agreement about the treatment of choice. Due to the inability of animals to produce keloid tissue, a standardised model to study the effects of different treatment modalities in vivo is lacking. Therefore, a comparative study on the effect of three pharmacological agents was conducted with human keloid implants in an athymic mouse model. MATERIAL AND METHODS: Cubic keloid tissue blocks from 10 human volunteers were implanted in 54 male, athymic, homozygotic mice. The animals were divided into 4 groups, including an untreated control group. Members of each section received either colchicine, nicardipine or

triamcinolone applied transdermally into the keloid tissue or into the peritoneum. The tissue specimens of 5 mice each were explanted according to a predetermined time schedule on days 28, 42 and 56 post-implantation and examined using various histological techniques including standard dye and immune histochemistry. The freeze-dried and moist weights of the keloid tissue were determined and analysed. RESULTS: Statistically significant changes regarding declining weight parameters were seen in the colchicines-treated group. Moreover, the densities of fibroblasts and endothelial cells were significantly reduced through colchicines treatment when compared to the control group and the groups treated with the other agents. The triamcinolone group also showed partially significant changes of weight compared to the control group, whereas no statistically significant effect of nicardipine on any parameter was found. Any influence of the host organism could be excluded as there were no signs of rejection or lymphocytic infiltration. CONCLUSION: Our study represents a successful attempt to create a standardised model for a comparative investigation on keloid tissue in vivo. The effect of colchicine was demonstrated in the light of an inhibitory effect on fibroblastic proliferative activity.
The studied model allows a direct comparison of implanted, vascularised keloid tissue and its reactivity to various agents without being biased by numerous unknown variables in humans.

Answer 3:

Bibliographic Information

Efficacy of pyridoxal treatment in controlling the growth of melanomas in cell culture and an animal pilot study. Maksymowych A B; Robertson N M; Litwack G Department of Pharmacology, Thomas Jefferson University, Philadelphia, Pennsylvania 19107 Anticancer research (1993), 13(6A), 1925-37. Journal code: 8102988. ISSN:0250-7005. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 8297098 AN 94127802 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

We have demonstrated, using confocal laser scanning microscopy, that pyridoxal treatment of B16C3 murine melanoma cells inhibits triamcinolone acetonide induced translocation of the glucocorticoid receptor to the nucleus of intact cells. In addition to inhibiting glucocorticoid receptor nuclear translocation, pyridoxal kills B16C3 murine melanoma cells and WM983A human melanoma cells in culture. Cortexolone, a glucocorticoid antagonist, also kills cells in culture. This mechanism, however, appears to initiate in the glucocorticoid receptor signal transducing cascade at a point prior to the impact of pyridoxal treatment alone. The glucocorticoid antagonist RU486 has no detrimental effect on melanoma cell viability, however, in combination with pyridoxal, RU486 extends cell viability. Since pyridoxal kills melanoma cells in culture, a pilot study was carried out examining the efficacy of topical application of a pyridoxal cream to inhibit the growth and/or cause regression of (B16C3) xenograft melanoma tumors in an immunocompetent (Hairless Rhino-J3) and an immunocompromised (Crl: nu/nu (CD1)BR) murine animal model. The results of the study with immunocompetent animals are encouraging. While tumors are brought under control by pyridoxal treatment, further work is needed to determine the most efficacious treatment regimen and to establish formal concentrations for pyridoxal in topical ointments. Trials using immunocompromised animals indicated that although some qualitative differences may be detected between the control and experimental animals, tumor growth in these animals is so aggressive that multiple applications or higher concentrations of pyridoxal may be needed to obtain useful data.

Answer 4:

Bibliographic Information

Evaluation of the effect of topical steroids on human scar contracture using a nude mouse model. Waymack J P; Robb E; Plessinger R; Warden G D; Alexander J W Shriners Burns Institute, Cincinnati Unit The Journal of burn care & rehabilitation (1988), 9(6), 640-2. Journal code: 8110188. ISSN:0273-8481. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 3065343 AN 89123607 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Adult nude mice had 1.5 to 1.0 meshed split-thickness human skin applied to an excised area of their back. The animals were then randomized into two groups, one of which had a steroid cream applied to their graft on alternate days. The other group had no ointment applied and served as a control. The wounds were measured on a weekly basis and the rate of wound contracture was found to be identical. Topical steroids would thus appear to offer no benefit in the prevention of scar contracture.

Answer 5:

Bibliographic Information

Effects of glucocorticoids on the growth of human fibrosarcoma cell line HT-1080. Walker M J; Lim C; Das Gupta T K; Beattie C W Cancer research (1986), 46(10), 4927-32. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 3756854 AN 87002051 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The human fibrosarcoma cell line HT-1080 exhibits rapid growth following s.c. inoculation in 4-6-week-old male athymic mice. Cytosols from tumors carried in athymic mice bind glucocorticoid (Kd, 1.8 +/- 0.48 X 10(-8) M; Bmax, 240.5 +/- 35.3 fmol/mg cytosol protein, mean +/- SEM). Receptor sediments primarily in the 8-9S region on 5-20% sucrose gradients and is specific for the glucocorticoids. HT-1080 growth in vitro (as measured by cell count) was inhibited over a range of 10(-6)-10(-8) M after 7 days of incubation with dexamethasone and triamcinolone acetonide. Progesterone, estradiol, and dihydrotestosterone had no effect on HT-1080 growth in vitro. Preincubation with a 100-fold excess of progesterone reversed the growth inhibition observed with triamcinolone acetonide but not dexamethasone acetate. HT-1080 tumor cell growth responded biphasically to dexamethasone in vivo. Athymic mice given s.c. injections every other day with 5 or 25 micrograms dexamethasone showed an increase in tumor size inversely proportional to dose. In contrast, 200 micrograms of dexamethasone significantly inhibited tumor growth. Adrenalectomy did not significantly alter HT-1080 growth or glucocorticoid binding to tumor cytosols (Kd, 3.4 X 10(-8) +/- 1.1, Bmax, 236.9 +/- 9.9 fmol/mg cytosol protein, mean +/- SEM) although tumor incidence was decreased in sham adrenalectomized mice. Glucocorticoid binding in tumors grown in vivo was decreased by increasing amounts of dexamethasone. High pharmacological doses of glucocorticoids inhibit the growth of human fibrosarcomas in vivo and in vitro.